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L19: Entry 1 of 3

File: USPT

Mar 28, 1995

US-PAT-NO: 5401508

DOCUMENT-IDENTIFIER: US 5401508 A

TITLE: Hydrogel compositions and structures made from same

DATE-ISSUED: March 28, 1995

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Manesis; Nick J.	San Jose	CA	N/A	N/A

US-CL-CURRENT: 424/427; 514/954, 523/113, 526/307.7, 623/6.56

AB: A hydrogel composition is disclosed which comprises water and a copolymer. In one embodiment, the copolymer is formed by reacting about 85% to about 99% by weight of at least one member selected from the group consisting of N,N-dimethylacrylamide, N,N-diethylacrylamide, N-methyl, N-ethylacrylamide and mixtures thereof; about 1% to about 15% by weight of at least one compound selected from the group consisting of alkyl acrylates, alkyl methacrylates and mixtures thereof wherein the alkyl group contains 1 to about 4 carbon atoms; and a minor, effective amount of at least one cross-linking agent. Such hydrogel compositions are effective as corneal inlays and onlays.

L19: Entry 2 of 3

File: USPT

Oct 15, 1985

US-PAT-NO: 4547327

DOCUMENT-IDENTIFIER: US 4547327 A

TITLE: Method for producing a porous prosthesis

DATE-ISSUED: October 15, 1985

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bruins; Paul F.	Brooklyn	NY	N/A	N/A
Ashman; Arthur	New York	NY	N/A	N/A

US-CL-CURRENT: 264/16; 264/112, 264/126, 264/19, 264/222, 433/201.1

AB: Small peptide mimics of TGF-.beta., having the general sequence AA.sub.i-AA.sub.i+1-AA.sub.i+2 followed by AA.sub.i+n shortly thereafter, have been prepared. In this sequence, AA.sub.i is alanine, asparagine, or leucine, AA.sub.i+1 is valine or isoleucine, AA.sub.i+2 is alanine, n is 3, 4, or 5 such that there are n-3 amino acid residues in between AA.sub.i+2 and AA.sub.i+n, and AA.sub.i+n is glutamic acid, aspartic acid, glutamine or asparagine. Because the essential requirement for TGF-.beta. activity is the peptide's ability to form a stable .beta.-bend structure under physiologic conditions, the inventive peptides are collectively referred to as .beta.-bend peptides. Compositions for applications such as tissue repair are also provided that comprise a biocompatible matrix having cytomodulin or a cytomodulin analog admixed with or carried by the matrix.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KMMC	Draw Desc	Image
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☐ 5. Document ID: US 5661127 A

L24: Entry 5 of 6

File: USPT

Aug 26, 1997

US-PAT-NO: 5661127

DOCUMENT-IDENTIFIER: US 5661127 A

TITLE: Peptide compositions with growth factor-like activity

DATE-ISSUED: August 26, 1997

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bhatnagar; Rajendra S.	Burlingame	CA	N/A	N/A
Qian; Jing Jing	San Bruno	CA	N/A	N/A

US-CL-CURRENT: 514/16; 530/329

AB: A peptide has been synthesized with the sequence ANVAENA (SEQ ID NO:1). This peptide, designated "cytomodulin," is able to mimic a broad range of activities of TGF-.beta.1 in various cell types. Compositions for applications such as tissue repair are provided that comprise a biocompatible matrix having cytomodulin admixed with or carried by the matrix.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KMMC	Draw Desc	Image
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☐ 6. Document ID: US 5522895 A

L24: Entry 6 of 6

File: USPT

Jun 4, 1996

US-PAT-NO: 5522895

DOCUMENT-IDENTIFIER: US 5522895 A

TITLE: Biodegradable bone templates

DATE-ISSUED: June 4, 1996

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mikos; Antonios G.	Houston	TX	N/A	N/A

US-CL-CURRENT: 623/23.58; 606/76, 606/77

AB: A biodegradable, bioresorbable, three-dimensional template for repair and replacement of diseased or injured bone which provides mechanical strength to bone while also providing a guide for growth of bone tissue. Preferably, the template is formed of biodegradable materials, for example, poly(L-lactic acid), poly(D, L-lactic acid), poly (D, L-lactic-co-glycolic acid), poly (glycolic acid), poly (.epsilon.-caprolactone), polyortho esters, and polyanhydrides, and has the capacity of being rendered porous, either in vitro or in vivo. A pore-forming component, which may or may not be a polymeric material, is mixed within a continuous matrix formed of a biodegradable material, the pore-forming component having a rate of degradation which exceeds that of the matrix. Differential dissolution or biodegradation provides porosity to the template.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KMC	Draw Desc	Image
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L19: Entry 2 of 3

File: USPT

Oct 15, 1985

DOCUMENT-IDENTIFIER: US 4547327 A

TITLE: Method for producing a porous prosthesis

## ABPL:

A porous implantable oral prosthesis which can be used to replicate and replace any hard tissue portion of the mouth such as bone and teeth is described. The prosthesis comprises sintered polymeric particles coated with a hydrophilic material. The polymeric particles vary in size so as to provide an area of relatively coarse porosity where the prosthesis is intended to interface with bone tissue and relatively fine porosity where it is intended to interface with soft tissue. A process for producing such prosthesis by filling a mold with appropriate molding compounds comprised of polymeric particles and a hydrophilic monomer, sintering the particles and polymerizing the monomer by dielectric heating, removing the sintered material from the cooled mold, and placing the prosthesis in a hot liquid to remove residues is described. An entire tooth, including a nonporous crown may be produced. A process for producing a porous replica of a tooth root suitable for implantation immediately after extraction of a tooth is disclosed. When extraction has taken place in the past and has resulted in the bone and gum receding, a porous implant inserted in a newly drilled hole in the patient's jaw bone may be used. A central post associated with the implant projecting above the gum may be used for attaching a denture, partial bridge or a crown. A porous implant may be used for jaw bone replacement in order to improve the fitting of dentures.

## BSPR:

The hydrophilic coatings swell but do not generally dissolve in body fluids. In order to assure that dissolution is prevented, a small quantity of cross-linking agent may be added to the polymer-monomer mixture, thus increasing the effective molecular weight of the polymerized hydrophilic material.

## DEPR:

A prosthesis may be produced by molding to predetermined sizes and shapes to fit a particular patient. The cavity of an appropriate mold is packed initially with coarse polymeric particles, which are coated with a hydrophilic material. In the process of the invention it is only necessary to pack the material utilizing strong manual pressure. A quantity of this material sufficient to form a portion of the implant which will interface with bone tissue is utilized leaving a portion of the mold cavity unfilled. This remaining volume is packed in a similar fashion with fine polymeric particles which are coated with a hydrophilic material, forming a portion of the implant which will interface with gum tissue. The packed mold is heated at atmospheric pressure in a dielectric oven where sintering of the PMMA and polymerization of the HEMA in the mold cavity occurs. After the mold has cooled, aided by immersion in cold water, the sintered prosthesis is removed from the mold and immersed in a hot liquid for a short period of time.

## DEPR:

A highly effective method of assuring adequate penetration, and therefore sufficient ingrowth of body tissue, an important feature of this invention, is the coating of the PMMA particles with a hydrophilic material. While many hydrophilic materials could conceivably be used, it has been found that polyhydroxyethylmethacrylate (PHEMA) is an excellent coating. Because of its hydrophilic nature, it will swell on exposure to body fluids but will not generally dissolve in these fluids.

## DEPR:

After two or three minutes of mixing the inhibited HEMA-PMMA mixture, with or without a cross linking agent, the PMMA particles become tacky and the HEMA physically penetrates into the PMMA surface, resulting in an excellent welding action during subsequent sintering, which produces a stronger implant than one resulting from the sintering of only PMMA particles. Where the HEMA coated particle surfaces meet, the polymerization and cross linking of the HEMA, which is chemical in nature, contributes to this result, producing a porous implant of exceptional strength.

CLPV:

(a) filling a portion of a mold cavity of the desired shape with relatively coarse polymeric particles coated with a hydrophilic monomer where said prosthesis is intended to interface with bone tissue;

CLPV:

(b) filling the remainder of said mold cavity with relatively fine polymeric particles coated with a hydrophilic monomer where said prosthesis is intended to interface with soft tissue;

CLPV:

(c) filling a portion of said mold cavity with relatively coarse polymeric particles coated with a hydrophilic monomer where said prosthesis is intended to interface with bone tissue;

CLPV:

(d) filling the remainder of said mold cavity with relatively fine polymeric particles coated with a hydrophilic monomer where said prosthesis is intended to interface with soft tissue;

CLPV:

(e) filling a portion of said first mold cavity with relatively coarse polymeric particles coated with a hydrophilic monomer where the root is intended to interface with bone tissue;

CLPV:

(f) filling the remainder of said first mold with relatively fine polymeric particles coated with a hydrophilic monomer where the root is intended to interface with soft tissue;

CLPV:

(a) filling a portion of a mold cavity of the desired shape with relatively coarse polymeric particles coated with a hydrophilic monomer where said prosthesis is intended to interface with bone tissue;

CLPV:

(b) filling the remainder of said mold cavity with relatively fine polymeric particles coated with a hydrophilic monomer where said prosthesis is intended to interface with soft tissue;

**WEST****End of Result Set**

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L19: Entry 3 of 3

File: USPT

Aug 20, 1985

DOCUMENT-IDENTIFIER: US 4536158 A

TITLE: Oral prosthesis and method for producing same

**ABPL:**

A porous implantable oral prosthesis which can be used to replicate and replace any hard tissue portion of the mouth such as bone and teeth is described. The prosthesis comprises sintered polymeric particles coated with a hydrophilic material. The polymeric particles vary in size so as to provide an area of relatively coarse porosity where the prosthesis is intended to interface with bone tissue and relatively fine porosity where it is intended to interface with soft tissue. A process for producing such prosthesis by filling a mold with appropriate molding compounds comprised of polymeric particles and a hydrophilic monomer, sintering the particles and polymerizing the monomer by dielectric heating, removing the sintered material from the cooled mold, and placing the prosthesis in a hot liquid to remove residues is described. An entire tooth, including a nonporous crown may be produced. A process for producing a porous replica of a tooth root suitable for implantation immediately after extraction of a tooth is disclosed. When extraction has taken place in the past and has resulted in the bone and gum receding, a porous implant inserted in a newly drilled hole in the patient's jaw bone may be used. A central post associated with the implant projecting above the gum may be used for attaching a denture, partial bridge or a crown. A porous implant may be used for jaw bone replacement in order to improve the fitting of dentures.

**BSPR:**

The hydrophilic coatings swell but do not generally dissolve in body fluids. In order to assure that dissolution is prevented, a small quantity of cross-linking agent may be added to the polymer-monomer mixture, thus increasing the effective molecular weight of the polymerized hydrophilic material.

**DEPR:**

A prosthesis may be produced by molding to predetermined sizes and shapes to fit a particular patient. The cavity of an appropriate mold is packed initially with coarse polymeric particles, which are coated with a hydrophilic material. In the process of the invention it is only necessary to pack the material utilizing strong manual pressure. A quantity of this material sufficient to form a portion of the implant which will interface with bone tissue is utilized leaving a portion of the mold cavity unfilled. This remaining volume is packed in a similar fashion with fine polymeric particles which are coated with a hydrophilic material, forming a portion of the implant which will interface with gum tissue. The packed mold is heated at atmospheric pressure in a dielectric oven where sintering of the PMMA and polymerization of the HEMA in the mold cavity occurs. After the mold has cooled, aided by immersion in cold water, the sintered prosthesis is removed from the mold and immersed in a hot liquid for a short period of time.

**DEPR:**

A highly effective method of assuring adequate penetration, and therefore sufficient ingrowth of body tissue, an important feature of this invention, is the coating of the PMMA particles with a hydrophilic material. While many hydrophilic materials could conceivably be used, it has been found that polyhydroxyethylmethacrylate (PHEMA) is an excellent coating. Because of its hydrophilic nature, it will swell on exposure to body fluid but will not generally dissolve in these fluids.



## DEPR:

After two or three minutes of mixing the inhibited HEMA-PMMA mixture, with or without a cross linking agent, the PMMA particles become tacky and the HEMA physically penetrates into the PMMA surface, resulting in an excellent welding action during subsequent sintering, which produces a stronger implant than one resulting from the sintering of only PMMA particles. Where the HEMA coated particle surfaces meet, the polymerization and cross linking of the HEMA, which is chemical in nature, contributes to this result, producing a porous implant of exceptional strength.

## CLPR:

1. An implantable prosthesis for hard tissue including a porous hard-tissue-ingrowth structure, the hard-tissue-ingrowth structure comprising a mass of polymeric particles, each particle having an inner core comprised of a first biologically-compatible polymeric material and having an outer coating generally surrounding the inner core, the outer coating being comprised of a second biologically-compatible polymeric material, the second material being hydrophilic and having a composition different from the composition of the first polymeric material, the particles being bonded together to form the hard-tissue-ingrowth structure, the hard-tissue-ingrowth structure having interstices between the bonded particles forming pores into which hard tissue can grow, the size of the particles of the hard-tissue-ingrowth structure being such that the pores of the structure have dimensions effective to promote the growth of hard tissue into the pores.

## CLPR:

2. The prosthesis according to claim 1 further including a soft-tissue-ingrowth structure comprising a mass of polymeric particles, each particle having an inner core comprised of the first biologically-compatible polymeric material and having an outer coating generally surrounding the inner core, the outer coating being comprised of the second hydrophilic biologically-compatible material, the particles being bonded together to form the soft-tissue-ingrowth structure, the soft-tissue-ingrowth structure having interstices between the bonded particles forming pores into which soft tissue can grow, the size of the particles of the soft-tissue-ingrowth structure being generally shorter than the size of the particles of the hard-tissue-ingrowth structure and being such that the pores of the soft-tissue-ingrowth structure have dimensions effective to promote the growth of soft tissue into the pores.

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L24: Entry 2 of 6

File: USPT

Feb 9, 1999

DOCUMENT-IDENTIFIER: US 5869080 A

TITLE: Absorbable implant materials having controlled porosity

## ABPL:

Absorbable implant materials having controlled porosity are formed by a method comprising the steps of: providing a dispersion of a bioabsorbable polymer, such as collagen, in a first solvent, such as water; adding particles of a second material, e.g. frozen water droplets or ice particles to the dispersion; followed by freezing the dispersion to form a frozen dispersion having the particles embedded therein, and removing both the first solvent and the second material from the frozen dispersion by freeze-drying or solvent extraction to leave the porous implant material. The invention also encompasses the use of such implant materials for wound healing applications.

## BSPR:

Various naturally occurring biopolymers, including proteins and polysaccharides, have been used over the last 20-30 years in the treatment of wounds or the augmentation of soft tissues. Proteins such as collagen, the most common animal protein and the main component of most connective tissues in the animal body, have been used due to their convenient physical properties and their high degree of bioacceptability. Collagen exists as many genetically distinct types, but the higher mammals share in common these types and the homology between the various types in, for example, man, cattle, sheep, pigs or chickens, is remarkably high. This means that the immunogenicity of animal collagens when implanted into humans, is very low and, therefore, that adverse reaction is very low. Furthermore, collagen and many other biopolymers actively assist wound healing by promoting the proliferation of fibroblasts, and by promoting angiogenesis.

## BSPR:

U.S. Pat. No. 4,970,298 (Frederick H. Silver et al) describes a biodegradable collagen matrix allegedly suitable for use as a wound implant. The matrix is formed by freeze drying an aqueous dispersion containing collagen, cross-linking the collagen via two cross-linking steps and freeze-drying the cross-linked matrix. The matrix may also contain hyaluronic acid and fibronectin.

## BSPR:

JP-A-03023864 (Gunze KK) describes a wound implant material comprising a collagen sponge matrix reinforced with fibres of poly-L-lactic acid. The collagen sponge matrix is formed by freeze drying a solution of porcine atherocollagen.

## BSPR:

EP-A-0562862 (Johnson & Johnson Medical, Inc.) describes bioabsorbable wound implant materials that are composites comprising a collagen sponge matrix having embedded therein oriented substructures of solid collagen fibers, films or flakes. The substructures reinforce the collagen sponge and also provide a scaffold for directional cellular migration into the implant. The composites are formed by immersing the substructures in an aqueous collagen slurry and then freeze-drying the slurry to form the collagen sponge matrix.

## BSPR:

Accordingly, the present invention provides a method of making a bioabsorbable implant material having interconnected pores comprising the steps of: providing a dispersion of a bioabsorbable polymer in a first solvent; adding particles of a second material to the dispersion; followed by freezing the dispersion to form a frozen dispersion having the particles embedded therein, and removing said first solvent and second material from said frozen dispersion.

## BSPR:

Removing both the first solvent and the second material from the frozen dispersion, for example by evaporation under vacuum (freeze drying), results in a solid bioabsorbable polymer comprising a sponge matrix having a structure somewhat similar to previously known bioabsorbable sponges, but also comprising therein larger interconnected pores corresponding in size and distribution to the dispersed particles in the frozen dispersion. Since the number and size of the particles in the frozen dispersion can readily be controlled, this method allows a sponge with high and controlled porosity to be made.

**WEST**☐ Generate Collection

L25: Entry 1 of 3

File: USPT

Dec 16, 1997

DOCUMENT-IDENTIFIER: US 5697976 A  
TITLE: Bioabsorbable implant material

## ABPL:

A porous bioabsorbable surgical implant material is prepared by coating particles of bioabsorbable polymer with tissue ingrowth promoter. Typical bioabsorbable polymers include polymers of glycolide, lactide, caprolactone, trimethylene carbonate, dioxanone, and physical and chemical combinations thereof. The tissue ingrowth promoter can include calcium hydroxide and/or a hydrophilic coating material. The hydrophilic coating material can be bioabsorbable or non-bioabsorbable. A typical non-bioabsorbable hydrophilic coating material is polyhydroxyethyl methacrylate (PHEMA). The bioabsorbable implant material may also contain a therapeutic agent. Typical therapeutic agents include an antimicrobial agent, dye, growth factors and combinations thereof.

## BSPR:

In one aspect of the present invention, particles of a bioabsorbable implant material, such as any of the commonly known bioabsorbable polymers, are coated with calcium hydroxide by placing the particles of implant material in a bed of calcium hydroxide powder in a container such as a flat pan, compacting the bed of calcium hydroxide, and heating the bed to a temperature sufficient to tackify the outer surface of the implant particles thereby causing at least some calcium hydroxide powder to adhere thereto. Compacting the bed of powder may be accomplished by placing the container in a flexible bag, applying a vacuum to the interior of the bag, and preferably thereafter sealing the bag. The bag with its contents can then be placed in an oven for heating.

## BSPR:

The aspects of the present invention are preferably combined. Thus, the bioabsorbable particles are first coated with calcium hydroxide and then coated with either the bioabsorbable or non-bioabsorbable hydrophilic coating material.

## DEPR:

The next step involves coating the beads with calcium hydroxide, which helps to stimulate bone and/or hard tissue ingrowth. The beads are mixed with calcium hydroxide and then heated to a temperature to make the bead surface sufficiently tacky to retain the calcium hydroxide particles. A preferred method of coating the beads is as follows:

## DEPR:

The washed beads are placed in a pan with a thin bed of calcium hydroxide powder. The beads are spread out and a thin layer of additional calcium hydroxide is poured over the top of the layer of beads making sure that all of the beads are sufficiently coated. The pan containing the beads is then placed in a heat sealable flexible bag such as a polyethylene bag and a vacuum is then applied to the interior of the bag and the bag is sealed. Application of the vacuum causes the bag to compress the calcium hydroxide-bead mixture into a compact mass. The sealed bag is then placed in an oven and the entire apparatus is subjected to a temperature and duration sufficient to tackify the outer surface of the beads, i.e., for glycolide/lactide polymers, (a temperature of from about 60.degree. C. to about 80.degree. C. for from about 1 to about 3 hours). Upon completion of the heating cycle the bag is taken out of the oven and permitted to cool to ambient temperature. The pan is then removed from the bag and the beads are separated from the calcium hydroxide by means of a sieve. The beads are then spray washed with sterile water two to five times to remove excess calcium hydroxide. The beads are then vacuum dried for 24 hours or longer. When beads are fabricated from bioabsorbable materials which are not hydrophilic, it is highly desirable to

from bioabsorbable materials which are not hydrophilic, it is highly desirable to coat the beads with a hydrophilic material to facilitate the permeation of body fluids into the implant to enable tissue ingrowth. Hydrophilic coatings facilitate tissue adhesion to the implant material and wetting of the implant by body fluids. Coatings are preferably from about 0.0001 inches to about 0.005 inches in thickness.

**WEST****End of Result Set**

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L25: Entry 3 of 3

File: USPT

Mar 1, 1988

DOCUMENT-IDENTIFIER: US 4728570 A

TITLE: Calcium-hydroxide-treated polymeric implant matrial

## ABPL:

An implant material for hard tissue comprising a porous matrix of a mass of biologically-compatible polymeric particles, the particles bonded together to form a unitary prosthetic implant, the prosthetic implant having interstices between the bonded particles forming pores into which bone tissue can grow and having a quantity of calcium hydroxide distributed in the pores of the matrix. Also disclosed is a packing material for forming in vivo prosthetic implants for hard tissue, the packing material comprising a mass of disjoint polymeric particles having an inner core and an outer coating and a quantity of calcium hydroxide distributed in the mass of polymeric particles effective to induce hard tissue growth.

## BSPR:

For many applications, it is preferred for the implant material of the invention to be in a granular form. Such a granular implant material can constitute a packing material for forming prosthetic implants for hard tissue in vivo. A preferred granular implant material comprises a mass of disjoint polymeric particles. Each particle has an inner core comprised of a first biologically-compatible polymeric material and has an outer coating comprised of a second biologically-compatible polymeric material which generally surrounds the inner core. The second polymeric material is hydrophilic and has a composition different from the composition of the first polymeric material. The polymeric particles are of a size to permit the mass of the disjoint particles to be packed in a body cavity to form a prosthetic implant for hard tissue with interstices between compacted particles of the prosthetic implant forming pores into which tissue can grow. The granular implant material of the invention further comprises a predetermined quantity of calcium hydroxide distributed in the mass of polymeric particles. The quantity of calcium hydroxide is effective to induce the growth of hard tissue in the pores of the mass of particles when packed in a body cavity. Preferably, the calcium hydroxide forms a coating on outer surfaces of the polymeric particles.

## DEPR:

Approximately 10 g of the PHEMA-coated PMMA beads described in subsection (1) was mixed with approximately 2 ml of the approximate 0.5 percent by weight calcium hydroxide solution described above. The beads were allowed to soak in the solution at room temperature for about 15-20 minutes. The beads were then separated from the solution by filtering and dried in a thin layer under a vacuum.

## DEPR:

PHEMA-coated PMMA beads treated with calcium hydroxide produced a graft which tended to induce bone formation in the gap (Table I, group 2). The new bone tissue thus formed produced a solid support. Cartilage and bone cells grew very close to the calcium-hydroxide treated PHEMA-coated PMMA beads, with substantially no intermediate layers of fibroblasts.

## DEPR:

Of all the Kiel bone implant materials, the most solid and mature bone bridge was formed by Kiel bone mixed with marrow, followed by Kiel bone treated with calcium hydroxide. In comparison to Kiel bone treated with calcium hydroxide, the PHEMA-coated PMMA beads treated with calcium hydroxide appeared to be superior,

since no fibroblast cellular interphase was seen between bone or cartilage. While the Kiel bone treated with calcium hydroxide induced much giant cell and macrophage response, the PHEMA-coated PMMA beads treated with calcium hydroxide did not induce any adverse cellular response.

CLPR:

18. The packing material according to claim 13 in which the calcium hydroxide forms a coating on outer surfaces of the polymeric particles.

CLPR:

19. The packing material according to claim 18 in which the coating of calcium hydroxide on the polymeric particles is formed by wetting the mass of polymeric particles with an aqueous solution of calcium hydroxide and then allowing the solution to dry.

CLPV:

(a) a mass of disjoint polymeric particles, each particle having an inner core comprised of a first biologically-compatible polymeric material and having an outer coating generally surrounding the inner core, the outer coating being comprised of a second biologically-compatible polymeric material, the second polymeric material being hydrophilic and having a composition different from the composition of the first polymeric material, the particles being of a size to permit the mass of the disjoint particles to be packed in a body cavity to form a prosthetic implant for hard tissue with interstices between compacted particles of the prosthetic implant forming pores into which tissue can grow; and

CLPV:

(b) a quantity of calcium hydroxide coated on the outer surfaces of said biologically-compatible polymeric particles, the quantity of calcium hydroxide being effective to induce the growth of hard tissue in the pores of the mass of the particles when packed in a body cavity.

**WEST**

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☐ 1. Document ID: US 5697976 A

L25: Entry 1 of 3

File: USPT

Dec 16, 1997

US-PAT-NO: 5697976

DOCUMENT-IDENTIFIER: US 5697976 A

TITLE: Bioabsorbable implant material

DATE-ISSUED: December 16, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chesterfield; Michael P.	Norwalk	CT	N/A	N/A
Torgerson; Robert D.	Branford	CT	N/A	N/A

US-CL-CURRENT: 424/423; 433/201.1, 606/76

AB: A porous bioabsorbable surgical implant material is prepared by coating particles of bioabsorbable polymer with tissue ingrowth promoter. Typical bioabsorbable polymers include polymers of glycolide, lactide, caprolactone, trimethylene carbonate, dioxanone, and physical and chemical combinations thereof. The tissue ingrowth promoter can include calcium hydroxide and/or a hydrophilic coating material. The hydrophilic coating material can be bioabsorbable or non-bioabsorbable. A typical non-bioabsorbable hydrophilic coating material is polyhydroxyethyl methacrylate (PHEMA). The bioabsorbable implant material may also contain a therapeutic agent. Typical therapeutic agents include an antimicrobial agent, dye, growth factors and combinations thereof.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWC	Draw Desc	Image
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☐ 2. Document ID: US 5366756 A

L25: Entry 2 of 3

File: USPT

Nov 22, 1994



US-PAT-NO: 5366756

DOCUMENT-IDENTIFIER: US 5366756 A

TITLE: Method for treating bioabsorbable implant material

DATE-ISSUED: November 22, 1994

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chesterfield; Michael P.	Norwalk	CT	N/A	N/A
Torgerson; Robert D.	Branford	CT	N/A	N/A

US-CL-CURRENT: 427/2.26; 424/426, 523/113, 525/937, 623/923

AB: A porous bioabsorbable surgical implant material is prepared by coating particles of bioabsorbable polymer with a tissue ingrowth promoter. Typical polymers include polymers of glycolide, lactide, caprolactone, trimethylene carbonate, dioxanone and physical and chemical combinations thereof. The tissue ingrowth promoter can include calcium hydroxide and/or a hydrophillic coating material. The hydrophillic coating material can be bioabsorbable or non-bioabsorbable. A typical non-bioabsorbable hydrophillic coating material is polyhydroxymethylmethacrylate (PHEMA). The bioabsorbable implant material may also contain a therapeutic agent. Typical therapeutic agents include an antimicrobial agent, dye, growth factor and combinations thereof. Typically, the particles are prepared by rotary atomization and coated by spraying.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	RMK	Draw Desc	Image
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☐ 3. Document ID: US 4728570 A

L25: Entry 3 of 3

File: USPT

Mar 1, 1988

US-PAT-NO: 4728570

DOCUMENT-IDENTIFIER: US 4728570 A

TITLE: Calcium-hydroxide-treated polymeric implant material

DATE-ISSUED: March 1, 1988

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ashman; Arthur	New York	NY	N/A	N/A
Binderman; Itzhak	Tel Aviv	N/A	N/A	ILX

US-CL-CURRENT: 428/327; 428/330, 606/76, 623/23.58

AB: An implant material for hard tissue comprising a porous matrix of a mass of biologically-compatible polymeric particles, the particles bonded together to form a unitary prosthetic implant, the prosthetic implant having interstices between the bonded particles forming pores into which bone tissue can grow and having a quantity of calcium hydroxide distributed in the pores of the matrix. Also disclosed is a packing material for forming in vivo prosthetic implants for hard tissue, the packing material comprising a mass of disjoint polymeric particles having an inner core and an outer coating and a quantity of calcium hydroxide distributed in the mass of polymeric particles effective to induce hard tissue growth.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	RMK	Draw Desc	Image
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Term	Documents
CALCIUM.USPT.	200956
CALCIUMS.USPT.	49
CALCIA.USPT.	1263
CALCIAS.USPT.	1
HYDROXIDE.USPT.	208975
HYDROXIDES.USPT.	47079
COAT\$	0
COAT.USPT.	88850
COATA.USPT.	19
COATABALITY.USPT.	1
((L9 OR L23) AND (CALCIUM HYDROXIDE WITH (COAT\$ OR LAYER)) ).USPT.	3

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L27: Entry 1 of 1

File: USPT

Feb 7, 1989

DOCUMENT-IDENTIFIER: US 4803075 A

TITLE: Injectable implant composition having improved intrudability

BSPR:

The present invention is in the field of body-treating compositions. More particularly it relates to injectable implant compositions for soft tissue augmentation that comprises an aqueous suspension of a particulate biocompatible material and a biocompatible fluid lubricant.

BSPR:

Several prior U.S. patents or applications that are owned or licensed to the assignee of the present invention relate to injectable collagen-based implants for soft tissue augmentation.

BSPR:

U.S. Pat. No. 3,949,073 describes the use of a solution of atelopeptide collagen as an injectable implant for augmenting soft tissue. The solution is brought to physiological ionic strength and pH and injected with a small gauge needle. The collagen fibers reconstitute to produce a fibrous mass of collagen at the injection site. Since the solid content of the injected material is low and the reconstituted fibers are flexible and small, there are no extrusion or intrusion problems with this material.

BSPR:

The present invention contemplates an injectable implant composition for soft tissue augmentation comprising an aqueous suspension amount of a biocompatible fluid lubricant to significantly improve the intrudability of the composition.

DEPR:

The two principal components of the injectable suspensions of the invention are: a biomaterial that provides the bulk of the implant and a biocompatible fluid that acts as a lubricant to improve the injectability of the biomaterial suspension. The biomaterial must meet several functional requirements in order to be useful as an implant for augmenting soft tissue. It must be nontoxic, well-tolerated by the body (i.e., produce no or tolerable levels of immune and inflammatory responses), and have mechanical properties that simulate those of soft tissue. It also must be relatively stable so that its properties do not significantly change in situ. Depending upon the body site at which the implant is placed, the material may also need to be relatively tough and elastic (i.e., capable of bearing loads without undergoing excessive or permanent deformation).

DEPR:

Examples of biomaterials that have been used or proposed for use in augmenting soft tissue are fibrillar cross-linked collagen, gelatin beads, and beads of natural or synthetic polymers such as polytetrafluoroethylene (TEFLON polymer), silicone rubber, and various hydrogel polymers such as polyacrylonitrile-polyacrylamide hydrogels. The fibrillar cross-linked collagen described in commonly owned U.S. Pat. No. 4,582,640 and U.S. patent application Ser. No. 715,098, the disclosures of which are incorporated herein by reference, is a preferred biomaterial for use in this invention.

DEPR:

The injectable implant compositions of this invention may be injected intradermally or subcutaneously into humans or other mammals to augment soft tissue, to correct congenital anomalies, acquired defects of cosmetic defects.

They may also be injected into internal tissues such as the tissue defining sphincters to augment such tissue. The specific uses of collagenous biomaterials for tissue augmentation are detailed in the above referenced commonly owned patents and applications.

## DEPR:

In terms of intrusion behavior, there were at least three classes of results: (1) Methylated collagen (bearing a positive charge), succinylated collagen (negative charge), and high molecular weight dextran sulfate (negative charge) facilitated flow of particulate cross-linked collagen, and very low levels (0.01% to 1% W/V) of lubricant were required; (2) There was a second class of uncharged polymers, such as dextran (Sample 5), heparin, and glycogen which facilitated flow, but at high concentration; and (3) The remaining polymeric samples are all uncharged and did not facilitate flow into porous beds.

## CLPR:

1. An injectable implant composition for soft tissue augmentation comprising an aqueous suspension of a particulate biomaterial containing a sufficient amount of a biocompatible fluid lubricant to significantly improve the intrudability of the composition, wherein said particles of biomaterial are fibrils or beads comprising natural or synthetic polymers, and wherein said fluid lubricant comprises a non-fibrillar high molecular weight charged polymer, a high molecular weight neutral polymer, or a low molecular weight neutral molecule.

## CLPR:

26. A method for augmenting soft tissue in a living mammal comprising injecting the composition of claim 1 into the mammal at the augmentation site.

## CLPR:

27. A method for augmenting soft tissue in a living mammal comprising injecting the composition of claim 8 into the mammal at the augmentation site.

## CLPR:

28. A method for augmenting soft tissue in a living mammal comprising injecting the composition of claim 9 into the mammal at the augmentation site.

## CLPR:

29. A method for augmenting soft tissue in a living mammal comprising injecting the composition of claim 11 into the mammal at the augmentation site.

## CLPR:

30. A method for augmenting soft tissue in a living mammal comprising injecting the composition of claim 12 into the mammal at the augmentation site.

**WEST**[Generate Collection](#)**Search Results - Record(s) 1 through 1 of 1 returned.**☐ **1. Document ID: US 4803075 A**

L27: Entry 1 of 1

File: USPT

Feb 7, 1989

US-PAT-NO: 4803075

DOCUMENT-IDENTIFIER: US 4803075 A

TITLE: Injectable implant composition having improved intrudability

DATE-ISSUED: February 7, 1989

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wallace; Donald G.	Menlo Park	CA	N/A	N/A
Reihanian; Hertsel	San Francisco	CA	N/A	N/A
Pharriss; Bruce B.	Palo Alto	CA	N/A	N/A
Braun; William G.	Los Altos	CA	N/A	N/A

US-CL-CURRENT: 424/423; 424/400, 514/18, 514/801, 514/802

AB: Injectable aqueous suspensions of biomaterials, such as cross-linked collagen, that contain a biocompatible fluid lubricant, such as glycogen or maltose, are disclosed. The inclusion of the lubricant significantly improves the intrusion of the suspension into soft tissue.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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Term	Documents
INJECTABLE.USPT.	25750
INJECTABLES.USPT.	2787
COLLAGEN.USPT.	18218
COLLAGENS.USPT.	1391
((9 OR 23) AND (INJECTABLE ADJ COLLAGEN)).USPT.	1

[Display](#)[50](#)Documents, starting with Document: [1](#)**Display Format:** [CIT, AB](#) [Change Format](#)

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L34: Entry 1 of 3

File: USPT

Jan 23, 2001

DOCUMENT-IDENTIFIER: US 6176874 B1

TITLE: Vascularized tissue regeneration matrices formed by solid free form fabrication techniques

## BSPR:

The macrostructure and porous parameters can be manipulated by controlling printing parameters, the type of polymer and particle size, as well as the solvent and/or binder. Porosity of the matrix walls, as well as the matrix per se, can be manipulated using SPF methods, especially 3DP. Structural elements that maintain the integrity of the devices during erosion can also be incorporated. For example, to provide support, the walls of the device can be filled with resorbable inorganic material, which can further provide a source of mineral for the regenerating tissue. Most importantly, these features can be designed and tailored using computer assisted design (CAD) for individual patients to individualize the fit of the device.

## DEPR:

Construction of a 3DP component can be viewed as the knitting together of structural elements that result from printing individual binder droplets into a powder bed. These elements are called microstructural primitives. The dimensions of the primitives determine the length scale over which the microstructure can be changed. Thus, the smallest region over which the concentration of bioactive agent can be varied has dimensions near that of individual droplet primitives. Droplet primitives have dimensions that are very similar to the width of line primitives formed by consecutive printing of droplets along a single line in the powder bed. The dimensions of the line primitive depend on the powder and the amount of binder printed per unit line length. A line primitive of 500 .mu.m width is produced if an ink jet depositing 1.1 cc/min of a solvent such as methylene chloride is made to travel at 8"/sec over a powdered polymer such as a polycaprolactone ("PLC") powder bed with between approximately 45 to 75 .mu.m particle size. Higher print head velocities and smaller particle size produce finer lines. The dimensions of the primitive seem to scale with that calculated on the assumption that the liquid binder or solvent needs to fill the pores of the region in the powder which forms the primitive.

## DEPR:

In the case of 3DP, a biocompatible material, preferably in particulate form, or as a porous sheet, is applied to a solid platform on a movable piston for solidification and/or incorporation of bioactive agent. A roller evenly spreads the particles over the platform bed. Solvent and/or binder is then selectively printed onto the polymer particles. After each layer is "printed", the piston lowers the polymeric material so that the process can be repeated to form the next layer.

## DEPR:

A number of materials are commonly used to form a matrix. Unless otherwise specified, the term "polymer" will be used to include any of the materials used to form the matrix, including polymers and monomers which can be polymerized or adhered to form an integral unit, as well as inorganic and organic materials, as discussed below. In a preferred embodiment the particles are formed of a polymer which can be dissolved in an organic solvent and solidified by removal of the solvent, such as a synthetic thermoplastic polymer, for example, ethylene vinyl acetate, poly(anhydrides), polyorthoesters, polymers of lactic acid and glycolic acid and other .alpha. hydroxy acids, and polyphosphazenes, a protein polymer, for example, albumin or collagen, or a polysaccharide. The polymer can be non-biodegradable or biodegradable, typically via hydrolysis or enzymatic

cleavage. Examples of non-polymeric materials which can be used to form the matrix include organic and inorganic materials such as hydroxyapatite, calcium carbonate, buffering agents, and lactose, as well as other common excipients used in drugs, which are solidified by application of adhesive or binder rather than solvent. In the case of polymers for use in making devices for cell attachment and growth, polymers are selected based on the ability of the polymer to elicit the appropriate biological response from cells, for example, attachment, migration, proliferation and gene expression.

DEPR:

For microstructures tailored to bone, inorganic powders in the final device increase the strength of the device and provide a source of minerals for the regenerating tissue. The strength requirements of soft tissues such as liver are substantially less than for bone, so greater void fractions in the final devices can be tolerated.

DEPR:

The binder can be a solvent for the polymer and/or bioactive agent or an adhesive which binds the polymer particles. Solvents for most of the thermoplastic polymers are known, for example, methylene chloride or other organic solvents. Organic and aqueous solvents for the protein and polysaccharide polymers are also known, although an aqueous solution, for example, containing a crosslinking agent such as carbodiimide or glutaraldehyde, is preferred if denaturation of the protein is to be avoided. In some cases, however, binding is best achieved by denaturation of the protein.

DEPR:

The selection of the solvent for the bioactive agent depends on the desired mode of release. In the case of an erodible device, the solvent is selected to either dissolve the matrix or is selected to contain a second polymer and/or a drug which is deposited. In the first case, the printed droplet locally dissolves the polymer powder and begins to evaporate. The drug is effectively deposited in the polymer powder after evaporation since the dissolved polymer is deposited along with the drug. The case where both the drug and a polymer are dissolved in the printed solution is useful in cases where the powder layer is not soluble in the solvent. In this case, binding is achieved by deposition of the drug polymer composite at the necks between the powder particles so that they are effectively bound together.

DEPR:

Aggressive solvents tend to nearly dissolve the particles and reprecipitate dense polymer upon drying. The time for drying is primarily determined by the vapor pressure of the solvent. There is a range from one extreme over which the polymer is very soluble, for example, 30 weight percent solubility, which allows the polymer to dissolve very quickly, during the time required to print one layer, as compared with lower solubilities. The degree to which the particles are attacked depends on the particle size and the solubility of the polymer in the solvent. Fine powder is more completely dissolved than powder with larger particle size.

DEPR:

The matrix material concentration in the binder solution will generally be at the limit of what can be accommodated by the nozzle, both to maximize the amount of matter delivered and to minimize migration of the solvent away from the ballistic impact point of the drop, thereby maximizing the resolution of the line width. The upper limit of polymer concentration is 15% for poly-L-lactic acid of 100,000 MW. This concentration of polymer may in some cases be insufficient in one-pass printing; devices made with larger powders may be cohesive with this amount of polymer. The amount of matter printed can be increased by including small latex or other particles in the printing solution. For example, polyglycolic acid (PGA) is not soluble in chloroform or ethyl acetate. Nanoparticles of PGA could be included in the printing solution (particles up to seven microns in diameter can be accommodated through the nozzle) to increase the polymer content which is printed. Latexes containing 30% by weight polymer (Eudragit.TM. are commercially available acrylic latexes) have been printed in existing machines without complications.

DEPR:

The amount of matter which is printed into the bed can also be increased by including small inorganic particles in the polymer solution, for example, bone

derived apatite.

DEPR:

Composite devices can be made by combining inorganic and organic components. In particular, it may be desired to increase the amount of matrix material in the device above that which can be obtained by one-pass printing of a solution of a matrix material into an inorganic powder bed, for example, by adding a polymer latex to the printing solution. Another method is to mix a polymer powder with an inorganic powder. Still another method is to spread only polymer powder in the bed, and print a dispersion of inorganic particles (up to 30 vol %) in a solvent which will bind the polymer powder together. An example of this is to print a solution of apatite particles in chloroform onto a PLA powder bed. Alternatively one can include a polymer binder with an inorganic dispersion, for example by adding 30% by volume particles to a 5% by weight solution of PLA in chloroform. In the extreme, the bed could contain no material at all; both the inorganic and organic material could be printed through the nozzle.

DEPR:

There are essentially no limitations on the bioactive agents that can be incorporated into the devices, although those materials which can be processed into particles using spray drying, atomization, grinding, or other standard methodology, or those materials which can be formed into emulsifications, microparticles, liposomes, or other small particles, and which remain stable chemically and retain biological activity in a polymeric matrix, are preferred.

DEPR:

Bioactive agents also include compounds having principally a structural role, for example, hydroxyapatite crystals in a matrix for bone regeneration. The particles may have a size of greater than or less than the particle size of the polymer particles used to make the matrix.

DEPR:

There are two principle methods for incorporation of bioactive agents: as a dispersion within a polymeric matrix and as discrete units within a discrete polymeric matrix. In the first case, the bioactive agent is preferably applied in the polymer particle binder; in the second, the bioactive agent is applied in a non-solvent for the polymer particles.

DEPR:

For example, the devices can be composed of particles of bioactive agent dispersed or embedded in a matrix of degradable polymer, such as PLA, PGA, and their copolymers (PLGAs). Implantation of the device is followed by slow hydrolysis and erosion of the polymer matrix. The release rate of bioactive agent is determined by the erosion rate of the polymer rather than just diffusion. Thus, the drug release rate can be controlled by the distribution of the drug throughout the matrix or by variation of the polymer microstructure so that the erosion rate varies with the position in the device. A drug concentration profile that is periodic with position away from the device surface will, for example, yield a drug release rate that is periodic in time as the polymer is eroded. The same effect can be achieved by periodic variation in polymer composition or porosity.

DEPR:

Structural elements made using the same or different polymeric particles can be designed within the device to provide physical structural support during degradation so as to avoid many of the problems associated with erodible devices. 3DP is used to create structural elements within the device formed by the solidification of the polymer particles, for example, by deposition of areas or regions of a different polymeric material, such as regions of a non-degradable polymer within regions of a degradable polymer.

DEPR:

(1) Printing a polymer solution onto a bed of particles which are not soluble in the polymer and which can be subsequently leached with a non-solvent for the polymer. In this case, the polymer which forms the device is printed onto a bed of particles such as salt, sugar, or polyethylene oxide. After the printing process is complete, the device is removed from the powder bed and placed in a nonsolvent for the polymer which will dissolve the particles. For example, polylactic acid in chloroform could be printed onto a bed of sugar particles, and



the sugar can subsequently be leached with water.

DEPR:

(2) Printing a polymer solution onto a bed of particles which are partially soluble in the printed solvent. An example is printing a polylactic acid solution onto a bed of polyethylene oxide particles. This procedure may allow interpenetration of PEO into the surface of the PLA and improve surface properties of the final device. Following printing, the PEO can be leached with water.

DEPR:

(5) Printing with solvents which have only a small solubility for the powder. In this manner only a small amount of polymer is deposited at the necks between the particles leaving much of the original porosity in the powder bed. For example, PCL is only slightly soluble in acetone and acetone has a relatively high vapor pressure. Very little polymer is, therefore, dissolved before the solvent dries. Thus, the necks formed between the particles are small and the porosity of the resulting component is much like that of the original powder bed.

DEPR:

Regeneration of native tissue structures can occur by stimulation of growth of neighboring, healthy tissue (e.g., healing a defect in bone) or may require transplantation of cells from another site, using either the patient's own tissue or that of a tissue-matched donor (e.g., growth of a new cartilage structure, replacement of liver). In either case, a device which serves as a scaffold or template to aid the growth of the new tissue is almost always necessary. The device can serve many functions, including: (1) as an immobilization site for transplanted cells, (2) formation of a protective space to prevent soft tissue prolapse into the wound bed and allow healing with differentiated tissue, (3) directing migration or growth of cells via surface properties of the device, and (4) directing migration or growth of cells via release of soluble molecules such as growth factors, hormones, or cytokines.

DEPR:

For the three applications described above, as well as for other applications in tissue regeneration which can be envisioned, 3DP offers at least three advantages over current technologies for processing biodegradable polymers: (1) tailored macroscopic shapes, (2) well-defined microstructure, which may include bimodal pore size distribution and directionally oriented pores and channels, (3) incorporation of growth factors during manufacture in order to provide controlled release of factors at specific sites, and (4) the ability to locally control surface properties in selected pores and channels to control cell adhesion, migration, and function from point to point within the device.

DEPR:

As used herein, "tissue" includes both soft tissues such as parenchymal tissue (liver, pancreas, intestine, and other tissues having metabolic functions), blood vessels, skin, and connective tissues such as cartilage and bone.

DEPR:

For microstructures tailored to soft tissues it is undesirable to have an inorganic powder as a component of the final device. However, printing a solution of a polymer such as PLA in chloroform or methylene chloride onto an inorganic powder bed or onto a bed of mixed polymer/inorganic is a technique for creating increased porosity in the final device if a water-soluble inorganic powder such as sodium chloride is used. The organic solvents can be removed by vacuum treatment, as is routinely done with manufacture of commercial drug-delivery devices. Supercritical carbon dioxide can also be used as a safe solvent to remove traces of chlorinated solvents. Solvent removal can be facilitated by allowing each layer to dry during the printing process, thereby reducing the length of time required under vacuum for subsequent solvent removal from the device.

CLPR:

5. The method of claim 1 wherein the solid free-form fabrication method is ballistic particle manufacturing or fusion deposition modeling and polymeric material is applied to a platform in layers to form a polymeric device.

CLPR:

6. The method of claim 1 wherein the solid free-form fabrication method is selective laser sintering comprising applying polymeric particles to a platform and fusing selected area of the polymeric particles with a laser.

CLPR:

20. The device of claim 16 wherein the solid free-form fabrication method is ballistic particle manufacturing or fusion deposition modeling and polymeric material is applied to a platform in layers to form a polymeric device.

CLPR:

21. The device of claim 16 wherein the solid free-form fabrication method is selective laser sintering comprising applying polymeric particles to a platform and fusing selected area of the polymeric particles with a laser.

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L34: Entry 1 of 3

File: USPT

Jan 23, 2001

US-PAT-NO: 6176874

DOCUMENT-IDENTIFIER: US 6176874 B1

TITLE: Vascularized tissue regeneration matrices formed by solid free form fabrication techniques

DATE-ISSUED: January 23, 2001

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vacanti; Joseph P.	Winchester	MA	N/A	N/A
Cima; Linda G.	Lexington	MA	N/A	N/A
Cima; Michael J.	Lexington	MA	N/A	N/A

US-CL-CURRENT: 623/1.44; 600/36, 623/1.39, 623/1.41, 623/901

AB: Solid free-form fabrication (SFF) methods are used to manufacture devices for allowing tissue regeneration and for seeding and implanting cells to form organ and structural components, which can additionally provide controlled release of bioactive agents, wherein the matrix is characterized by a network of lumens functionally equivalent to the naturally occurring vasculature of the tissue formed by the implanted cells, and which can be lined with endothelial cells and coupled to blood vessels at the time of implantation to form a vascular network throughout the matrix. The SFF methods can be adapted for use with a variety of polymeric, inorganic and composite materials to create structures with defined compositions, strengths, and densities, using computer aided design (CAD). Examples of SFF methods include stereo-lithography (SLA), selective laser sintering (SLS), ballistic particle manufacturing (BPM), fusion deposition modeling (FDM), and three dimensional printing (3DP).

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 2. Document ID: US 6139574 A

L34: Entry 2 of 3

File: USPT

Oct 31, 2000

US-PAT-NO: 6139574

DOCUMENT-IDENTIFIER: US 6139574 A

TITLE: Vascularized tissue regeneration matrices formed by solid free form fabrication techniques

DATE-ISSUED: October 31, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vacanti; Joseph P.	Winchester	MA	N/A	N/A
Cima; Linda G.	Lexington	MA	N/A	N/A
Cima; Michael J.	Lexington	MA	N/A	N/A

US-CL-CURRENT: 623/1.44; 600/36, 623/1.39, 623/1.41, 623/901

AB: Solid free-form fabrication (SFF) methods are used to manufacture devices for allowing tissue regeneration and for seeding and implanting cells to form organ and structural components, which can additionally provide controlled release of bioactive agents, wherein the matrix is characterized by a network of lumens functionally equivalent to the naturally occurring vasculature of the tissue formed by the implanted cells, and which can be lined with endothelial cells and coupled to blood vessels at the time of implantation to form a vascular network throughout the matrix. The SFF methods can be adapted for use with a variety of polymeric, inorganic and composite materials to create structures with defined compositions, strengths, and densities, using computer aided design (CAD). Examples of SFF methods include stereo-lithography (SLA), selective laser sintering (SLS), ballistic particle manufacturing (BPM), fusion deposition modeling (FDM), and three dimensional printing (3DP).

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 3. Document ID: US 4863472 A

L34: Entry 3 of 3

File: USPT

Sep 5, 1989

US-PAT-NO: 4863472

DOCUMENT-IDENTIFIER: US 4863472 A

TITLE: Bone graft implant

DATE-ISSUED: September 5, 1989

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Tormala; Pertti	Tampere	N/A	N/A	FIX
Rokkanen; Pentti	Helsinki	N/A	N/A	FIX
Oikarinen; Valle J.	Helsinki	N/A	N/A	FIX
Vainionpaa; Seppo	Helsinki	N/A	N/A	FIX
Helevirta; Pertti	Tampere	N/A	N/A	FIX

US-CL-CURRENT: 623/23.58; 433/201.1

AB: Supporting structure (1) for preventing the movements of powder material (2) which will be applied as bone graft (bone graft powder) which supporting structure (1) will be located to contact with bone tissue and which supporting structure (1) is manufactured of at least partially resorbable polymer, copolymer or polymer mixture and is of its form chutelike, box-like, a flat tube or bag and contains such open porosity, which allows the surrounding tissues to grow through the supporting structure (1) but which prevents the migration of the bone graft powder (2) through the pores outside the supporting structure (1). The part of the supporting (1) which will be located against bone surface contains at least one orifice, whose size is bigger than the size of pores of the supporting (1) and bigger than the size of the bone graft powder (2) particles, which orifice makes possible the growth of the bone tissue into the inside of the supporting structure (1).

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	INAC	Draw. Desc	Image
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Term	Documents
SOFT.USPT.	203232
SOFTS.USPT.	23
TISSUE.USPT.	122702
TISSUES.USPT.	62329
(33 AND (SOFT ADJ TISSUE)).USPT.	3

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L38: Entry 2 of 19

File: USPT

Jun 6, 2000

DOCUMENT-IDENTIFIER: US 6071530 A

TITLE: Method and composition for treating a bone tissue defect

## BSPR:

To preclude surgical removal of an implant, membranes made of bioabsorbable material, such as microfibrillar collagen, polylactic acid, and polygalactin (Vicryl.RTM.) mesh have been used. Fitting and positioning these membranes to the implant site is cumbersome and time-consuming, and the therapeutic effect of these membranes has been unpredictable. In addition, the degradation time of membranes composed of collagen has been variable, and the risk of adverse immunological reaction to this foreign protein material in the body presents a major concern.

## BSPR:

The implant precursor may be applied to an implant site in an animal, such as a void, a defect, surgical incision, and the like, in or on a hard or soft tissue. Once placed in the implant site, the implant precursor eventually forms a solid microporous implant by the dissipation of the organic solvent into surrounding tissue fluids and the further coagulation of the polymer. Preferably, the matrix of the resulting implant has a two-layered pore structure with a highly porous inner core portion and a comparatively less porous outer surface layer or skin. Pores are formed in the solid matrix of the implant by dissipation of the solvent out of the composition into surrounding tissue fluids. Optionally, the implant precursor may include a separate pore-forming agent that is capable of generating pores within the polymer matrix of the solid implant, as for example, sucrose, sodium chloride, a cellulose-based polymer, and the like.

## BSPR:

As used herein, the term "implant site" is meant to include a site, in or on which the implant precursor is formed or applied, as for example, a soft tissue such as muscle or fat, or a hard tissue such as bone. Examples of implant sites include a tissue defect such as a tissue regeneration site; a void space such as a periodontal pocket, surgical incision or other formed pocket or cavity; a natural cavity such as the oral, vaginal, rectal or nasal cavities, the cul-de-sac of the eye, and the like; and other sites into which the implant precursor may be placed and formed into a solid implant. The term "biodegradable" means that the polymer and/or polymer matrix of the implant will degrade over time by the action of enzymes, by hydrolytic action and/or by other similar mechanisms in the human body. By "bioerodible," it is meant that the implant matrix will erode or degrade over time due, at least in part, to contact with substances found in the surrounding tissue fluids, cellular action, and the like. By "bioabsorbable," it is meant that the polymer matrix will be broken down and absorbed within the human body, for example, by a cell, a tissue, and the like.

## DEPR:

The size or diameter of the pores formed in the matrix of the solid implant may be modified according to the size and/or distribution of the pore-forming agent within the polymer matrix. For example, pore-forming agents that are relatively insoluble in the polymer mixture may be selectively included in the polymer composition according to particle size in order to generate pores having a diameter that corresponds to the size of the pore-forming agent. Pore-forming agents that are soluble in the polymer mixture may be used to vary the pore size and porosity of the implant matrix by the pattern of distribution and/or aggregation of the pore-forming agent within the polymer mixture and coagulating and solid polymer matrix.

## DEPR:

The biologically-active agent may stimulate a biological or physiological activity with the animal. For example, the agent may act to enhance cell growth and tissue regeneration, function in birth control, cause nerve stimulation or bone growth, and the like. Examples of useful biologically-active agents include a substance, or metabolic precursor thereof, which is capable of promoting growth and survival of cells and tissues, or augmenting the functioning of cells, as for example, a nerve growth promoting substance such as a ganglioside, a nerve growth factor, and the like; a hard or soft tissue growth promoting agent such as fibronectin (FN), human growth hormone (HGH), protein growth factor interleukin-1 (IL-1), and the like; a bone growth promoting substance such

## DEPR:

The implant precursor may be used for treating a variety of tissue defects. The implant precursor may be applied to an implant site in an animal, such as a void, a defect, surgical incision, and the like, in a hard or soft tissue, by known surgical techniques.

## DEPR:

For example, the implant precursor may be used in a method for treating a bone tissue defect such as an arm or leg bone fracture, a tooth defect, and the like. Preferably, the bone tissue is surgically separated from the adjacent soft tissue to expose the defect, and the implant precursor is placed into the bone defect, whereupon the implant precursor hardens in situ to a solid implant.

## DEPR:

In a preferred use according to the invention, the implant precursor may be used as a barrier system for guided tissue regeneration. The implant precursor may be formed outside the body of the animal and then administered to an implant site such as a tissue with a void such as a periodontal pocket, a soft-tissue defect, a surgical incision, a bone defect and the like. Once administered to the tissue regeneration site, the implant precursor will solidify to form a solid, microporous matrix that provides a surface over which the cell may grow. To enhance regeneration of a hard tissue such as bone tissue, it is preferred that the solid implant matrix provides support for new cell growth that will replace the matrix as it becomes gradually absorbed or eroded by body fluids.

## DEPR:

A thigh bone of an anesthetized male rat may be surgically incised to create a defect and granules of Surgicel.TM. oxidized cellulose may be applied to the defect to stop the bleeding and to fill in the defect. A polymer mixture prepared according to Example 1 may then be applied directly over the surface of the Surgicel.TM. support layer. The moisture from the tissue defect will cause the liquid polymer to partially solidify to form the same type of implant precursor as described in Example 1. The soft tissue is then replaced and sutured into place. The implant precursor thus formed will further solidify to a solid barrier matrix.

**WEST**

Generate Collection

L38: Entry 3 of 19

File: USPT

Aug 31, 1999

DOCUMENT-IDENTIFIER: US 5945115 A

TITLE: Polymeric compositions useful as controlled release implants

BSPR:

Other additives can be used to advantage in further controlling the desired release rate of a bioactive material for a particular treatment protocol. For example, if the thermoplastic polymer liquid composition is too impervious to water, a pore-forming agent can be added to generate additional pores in the matrix. Any biocompatible water-soluble material can be used as the pore-forming agent. These agents can be either soluble in the liquid composition or simply dispersed within it. They are capable of dissolving, diffusing or dispersing out of both the coagulating polymer matrix and the formed polymer system whereupon pores and microporous channels are generated in the matrix and system. The amount of pore-forming agent (and size of dispersed particles of such pore-forming agent, if appropriate) within the composition will directly affect the size and number of the pores in the polymer system.

BSPR:

Administration of the liquid composition or the externally formed polymer system of the invention ultimately will be accomplished according to the wisdom and protocol of the patient's attending health care professional such as a physician, or if appropriate, a dentist or DVM. Choice of the particular composition will depend upon the condition to be treated, which choice will be made by the attending health care professional. When the liquid composition is injected into soft tissue to provide a sustained release implant, the resulting polymer system will both release the bioactive material and biodegrade as designed so that no residue remains. When the liquid composition is injected into a soft tissue defect and a suitable bioactive material for assisting in collagen formation is in the composition, the resulting polymer system fills the defect and provides a support structure upon which natural collagen tissue can grow. This collagen tissue gradually replaces the biodegradable polymer. With hard tissue such as bone, the biodegradable polymer containing a bone growth factor supports the growth of new bone cells. These new bone cells eventually replace the degrading polymer.



**WEST**

Generate Collection

L38: Entry 9 of 19

File: USPT

Feb 25, 1997

DOCUMENT-IDENTIFIER: US 5605693 A  
TITLE: Methods of making a porous device

## BSPR:

The applications and uses of synthetic biocompatible implements and devices adapted for implantation or installation in or on a human body have dramatically increased in recent years. Such implements and devices include soft tissue implants for use, for example, in breast augmentation, chin, nose, ear and other body part reconstruction and the like, nerve cuffs and scaffolds, lymphedema shunts, percutaneous skin and blood access devices, insulin cell producing implants and other cell sequestering cage devices, artificial tendon and ligament and tendon and ligament repair prostheses, artificial heart and vascular prostheses, burn dressings, and drug infusing, releasing or delivery devices.

## BSPR:

Oftentimes, devices of the type described above fail due to problems at the implant-tissue interface. As early as 1970, Homsey, recognized that if the implant size is in the order of centimeters, a "fibrocartilaginous" membrane or capsule isolates the implant from normal tissue. If the implant is perforated so that the interstices (pores and pore interconnections) are of the order of 1 mm or less, the implant becomes woven with the tissue, rather than encapsulated as above (Homsey, C. A., 1970, J. Biomed. Mater. Res., 4:341-356). Smooth-walled silicone breast implants fail in the order of 40-60 percent due to this thick "fibrocartilaginous" membrane (capsule) which forms around the implant creating a hard, inelastic, and often painful feeling implant. This fibrous capsule also creates other problems around implants in general because it is composed mainly of dense compacted collagen, and fibroblasts, with little or no vascularity. This leads to isolation of the implant, the implant-capsule interface, and the capsule itself from the nutrient, metabolic, and cellular advantages of good blood supply, making the implant site more prone to infection, and the infections less amenable to treatment by natural resistance mechanisms and/or blood borne antibiotics.

## BSPR:

Previous approaches to forming porous materials (for implants or other uses) have typically included use of bubble-forming technology, sintering of metal or polymer particles into a partially fused body, expansion of polymer melts or solutions (such as used to produce Gortex), processing fibers to produce fabric felts, velours, meshes or weaves, and replicating or duplicating the microstructure of carbonate animal skeletal material. See, for example, White, R. A., Weber, J. N. and White, E. W., "Replanineform: A New Process for Preparing Porous Ceramic, Metal, and Polymer Prosthetic Materials," Science, Vol. 176, pp. 922-924; U.S. Pat. No. 3,890,107; Leidner, J. et al., "A Novel Process for the Manufacturing of Porous Grafts: Process Description and Product Evaluation," Journal of Biomedical Materials Research, Vol. 17, pp. 229-247 (1983). Among the problems of using bubble technology to produce porous materials is the difficulty of separately controlling pore size, pore shape, and pore interconnections. Also, the resulting pores typically include sharp edges and terminations which can cause accelerated inflammation and thus problems and/or discomfort when implanted. The sintering and polymer expansion approaches are limited to the use of only certain kinds of materials, typically metals for sintering and polytetrafluoroethylene for polymer expansion, and these may not be materials having the desired flexibility, resiliency, biocompatibility, or the like. The processing of fibers limited because only materials which can be made into fibers can be used, and the resulting structure is basically two-dimensional. The replication of carbonate animal skeletal material, although suitable for some

uses, requires milling of the material to the desired size and shape, and again the pore size and shape cannot be controlled.

DEPR:

The vascular prostheses described above may be implanted into subcutaneous or intra-muscular positions. After the prosthesis walls become filled with tissue (from several minutes [pre-clotting] to several days [cell seeding] to several weeks [tissue ingrowth] depending on the type of tissue desired), the prosthesis may be removed from its position and transplanted as a composite (composed of two types of material--tissue and polymer) graft into the recipient site, in this case a blood vessel. In this way, a vascular graft composed of tissue (as well as polymer) can be used as a live autogenous graft without creating the donor-site morbidity of sacrificing a blood vessel. In a similar fashion, many types of tissue may be transplanted including bone marrow, liver, pancreas, collagen, or neovascularity or any tissue or cell culture which can be made to grow into the porosity of the implant.

ORPL:

Taylor, S. R. "Effect of surface Texture on the Soft Tissue Responses to Polymer Implants," (1983) pp. 205-227.

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L38: Entry 18 of 19

File: USPT

Dec 23, 1986

DOCUMENT-IDENTIFIER: US 4631188 A

TITLE: Injectable physiologically-acceptable polymeric composition

BSPR:

Polymeric implants are formed in defined shapes and sizes as demanded by the specific application. Such preshaped forms have several disadvantages. Most significantly, the applications require surgical procedures. Secondly, a polymeric implant, as a rule, is encapsulated by collagenous tissue capsule and is not integratable into surrounding tissue; porous polymeric implants may be connected to surrounding tissue by in-growing cells, however, such porous polymeric implants are often prone to calcification, etc. Thirdly, the size and shape of the polymeric implant must be determined in advance and any changes of size and shape are affected by re-implantation.

BSPR:

More recent attempts regarding solidifying compositions utilized an aqueous solution of purified bovine collagens which are injected into the tissue and which gelatinate when heated above 37.degree. C. by collagen transition into fibrillar form without presence of low molecular weight toxic components. Collagen itself, however, is reactive and is gradually degraded by enzymatic reaction and is resorbed after a period of time. Thus, such a gelatinous implant is only a temporary replacement of a pre-formed implant which may be subsequently replaced by natural tissue. There is little control over such natural replacement, and unsatisfactory results occur in many instances.

BSPR:

The polymeric compound is admixed with the solvent in a concentration of from about 0.1 to 50% by weight, such that the resulting polymeric solution when in contact with water forms an integral solid (homogeneous or porous), and in no event forms a dispersion of solid polymer particles. In other words, the polymeric solution coagulates rather than precipitates when its contacts water. Such coagulation property is related to the solution viscosity, which is, in turn, determined by the molecular weight of the polymeric compound, its concentration and temperature. The viscosity of these compositions ranges from about 15 centipoises to about 20,000 centipoises. The concentration of the polymeric compound with solvent suitable for an injectable polymeric composition decreases with increasing molecular weight of the polymeric compound. Coagulation of the polymeric compound in contact with water is reversible, and is a purely physical process without any associated chemical change in the polymeric compound. The coagulated polymeric compound can be redissolved in the same or a similar solvent.

BSPR:

The polymeric composition of the present invention may also include a biologically active substance to effect certain results, e.g. thrombin may be added to effect coagulation at the injected site, collagen may be added to provide a support site, etc. Advantageously, any such biologically active substance should be substantially soluble in the solvent or solvent system but essentially insoluble in water.

BSPR:

True hydrogels (swelling to an equilibrium in contact with water) are particularly advantageous for replacement and augmentation of soft tissue, as a filler of body cavities and the like. Such a hydrogel is elastic with elasticity increasing with increasing water content. Additionally water uptake compensates for loss of solvent. The resulting hydrogel formed in the tissue may have a lower or higher volume than the injected solution, depending upon the solution

**WEST****Generate Collection****Search Results - Record(s) 1 through 6 of 6 returned.**☐ 1. Document ID: US 5885829 A

L24: Entry 1 of 6

File: USPT

Mar 23, 1999

US-PAT-NO: 5885829

DOCUMENT-IDENTIFIER: US 5885829 A

TITLE: Engineering oral tissues

DATE-ISSUED: March 23, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mooney; David J.	Ann Arbor	MI	N/A	N/A
Rutherford; Robert B.	Ann Arbor	MI	N/A	N/A

US-CL-CURRENT: 435/325; 424/422, 424/435, 424/49, 435/374, 435/378, 435/69.1

AB: Disclosed are methods for regenerating dental and oral tissues from viable cells using ex vivo culture on a structural matrix. The regenerated oral tissues and tissue-matrix preparations thus provided have both clinical applications in dentistry and oral medicine and are also useful in in vitro toxicity and biocompatibility testing.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 2. Document ID: US 5869080 A

L24: Entry 2 of 6

File: USPT

Feb 9, 1999

US-PAT-NO: 5869080

DOCUMENT-IDENTIFIER: US 5869080 A

TITLE: Absorbable implant materials having controlled porosity

DATE-ISSUED: February 9, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
McGregor; James	Glasgow	N/A	N/A	GBX
Watt; Paul W.	East Kilbride	N/A	N/A	GBX
Light; Nicholas D.	Perthshire	N/A	N/A	GBX
Harvey; Wilson	Stirling	N/A	N/A	GBX

US-CL-CURRENT: 424/426

AB: Absorbable implant materials having controlled porosity are formed by a method comprising the steps of: providing a dispersion of a bioabsorbable polymer, such as collagen, in a first solvent, such as water; adding particles of a second material, e.g. frozen water droplets or ice particles to the dispersion; followed by freezing the dispersion to form a frozen dispersion having the particles embedded therein, and removing both the first solvent and the second material from the frozen dispersion by freeze-drying or solvent extraction to leave the porous implant material. The invention also encompasses the use of such implant materials for wound healing applications.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWMC	Draw Desc	Image
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☐ 3. Document ID: US 5863551 A

L24: Entry 3 of 6

File: USPT

Jan 26, 1999

US-PAT-NO: 5863551

DOCUMENT-IDENTIFIER: US 5863551 A

TITLE: Implantable polymer hydrogel for therapeutic uses

DATE-ISSUED: January 26, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Woerly; Stephane	Quebec	N/A	N/A	CAX

US-CL-CURRENT: 424/423; 424/487, 424/78.08, 523/113, 526/199, 526/200

AB: The hydrogel is a copolymer of an N-substituted methacrylamide or acrylamide, a cross-linking agent and a complex sugar or derivative, a tissue adhesion peptide or a polymer conjugate with antibodies, the polymer being heterogeneous, elastically deformable and having an equilibrium water content of at least about 80%. It can be used for tissue regeneration and for organ repair, for example, in the developing and adult nervous system.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWMC	Draw Desc	Image
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☐ 4. Document ID: US 5780436 A

L24: Entry 4 of 6

File: USPT

Jul 14, 1998

US-PAT-NO: 5780436

DOCUMENT-IDENTIFIER: US 5780436 A

TITLE: Peptide compositions with growth factor-like activity

DATE-ISSUED: July 14, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bhatnagar; Rajendra S.	Burlingame	CA	N/A	N/A
Qian; Jing Jing	San Bruno	CA	N/A	N/A

US-CL-CURRENT: 514/18; 514/17, 530/329, 530/330